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Use of Lymphoblastoid Cell Lines to Evaluate the Hypersensitivity to Ultraviolet Radiation in Cockayne Syndrome

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Cockayne syndrome (CS) is a rare autosomal recessive disease characterized by acute sun sensitivity, cachectic dwarfism, and neurologic and skeletal abnormalities. Cultured skin fibroblasts from patients with this disease are known to be hypersensitive to the lethal effects of 254-nm UV radiation. We have studied the sensitivity to 254-nm UV radiation of lymphoblastoid lines derived from 3 typical CS patients, 1 atypical CS patient who had a very late age of onset of clinical manifestations, 2 patients who had both xeroderma pigmentosum (XP) and typical CS, and 3 heterozygous parents of these patients. Post-UV survival was determined by the trypan-blue dye-exclusion method.

The lymphoblastoid lines from the 3 typical CS patients, the atypical CS patient, and the 2 patients with both CS and XP had decreased post-UV viability in comparison with lines from normal donors. Lines from the heterozygous parents had normal post-UV viability. The post-UV viability of the typical CS lines was similar to that of a XP complementation group C line. The relative post-UV viability of lymphoblastoid lines from the typical CS patients was similar to the relative post-UV survival of their fibroblast lines. The lymphoblastoid line from the atypical CS patient had a post-UV viability similar to that of the typical CS patients. Thus, the relative hypersensitivity of CS patients' cells in vitro does not reflect the severity or age of onset of the patients' clinical manifestations. The lymphoblastoid lines from the 2 patients who had both CS and XP were significantly more sensitive to the UV radiation than those from patients with only CS.

Our studies demonstrate that lymphoblastoid lines from patients with CS are appropriate and useful cell lines for the study of the inherited hypersensitivity to UV radiation.

Cockayne syndrome (CS) is a rare autosomal recessive disease characterized by acute sun sensitivity, cachectic dwarfism, skeletal abnormalities, pigmentary retinal degeneration, and progressive neurologic defects including dementia [1–6]. Cultured skin fibroblasts from CS patients are hypersensitive to the lethal effects of 254-nm UV radiation [7,8] but have no detectable defects in nucleotide excision repair [6–9] or postreplication repair [9,10]. Fibroblasts from patients with xeroderma pigmentosum (XP), another rare autosomal recessive disease, also show a hypersensitivity to UV radiation [6,11–13]. However, most XP fibroblasts are deficient in nucleotide excision repair [6,12,13] and in postreplication repair [6, 13–15].

Epstein-Barr virus-transformed lymphoblastoid lines derived from peripheral blood B lymphocytes have proved very useful in studying the inherited hypersensitivity of XP cells to 254-nm UV radiation [16]. We therefore studied lymphoblastoid lines derived from several CS patients to determine (1) whether the lines manifest the CS phenotype of cellular hypersensitivity to UV radiation in terms of cell survival, (2) whether such cellular hypersensitivity can be reliably quantified, and (3) whether the degree of hypersensitivity to UV radiation reflects the severity or age of onset of the patients' clinical abnormalities.

We studied lymphoblastoid lines from 3 typical CS patients, 1 atypical CS patient who had a late age of onset and mild clinical features, 2 patients known to have both XP and CS, and 3 heterozygous parents of these patients.

MATERIALS AND METHODS

Lymphoblastoid Lines

All the lymphoblastoid lines were derived by transforming peripheral blood lymphocytes with Epstein-Barr virus. All lines are available from The Human Genetic Mutant Cell Repository, Copewood and Davis Streets, Camden, New Jersey. The patients' lymphoblastoid lines used for post-UV survival experiments are presented in Table I. Table II compares the relevant clinical features of 2 of the typical CS patients with the features of the atypical CS patient. The lymphoblastoid lines from normal controls used for post-UV survival experiments were GM 333, 536, 558, 606, 621, 892, 923, and RB 4580. Additional lines used for post-x-ray survival experiments were as follows: 22 normal: GM 130, 333, 536, 558, 606, 621, 892, 923, 1056, 1310, 1956, 2148, 3928, RB 4083, 4467, 4469, 4579, 4580, 4604, 5830, E-1, R-1; ataxia telangiectasia: GM 717, 1526; ataxia telangiectasia heterozygote: GM 3187, 3188.

Culture and Irradiation Technique

The lymphoblastoid lines were cultured and irradiated as described previously [16,25]. The lines were maintained in stock cultures at concentrations between 2×10^5 and 3×10^6 cells/ml at 37°C in a humidified atmosphere of 5% CO_2:95% air in RPMI medium 1640 (Gibco) containing 20% fetal bovine serum (Gibco). The mean growth rate of the unirradiated normal lines was not significantly different from that of the patient lines. Half an hour before irradiation, 0.5 ml of the cell suspension was mixed with 1.5 ml of trypan-blue solution (0.4% in normal saline, Gibco) and the viable (i.e., trypan-blue-excluding) cells were counted in a hemocytometer.

For post-UV survival experiments the culture medium was centrifuged at 600 *g* for 10 min, and the cells were resuspended to a concentration of approximately 3.2×10^6/ml of Hanks' balanced salt solution (without phenol red). The cells were then irradiated with 254-nm UV radiation at a flux of 0.08 J/m^2 from a germicidal lamp (General Electric, No. G15T8). Immediately after the time of irradiation, each volume of the cell suspension was diluted with 7 volumes of fresh medium, and the cells were incubated for 3 days, when the viable cells were determined by the trypan-blue-exclusion method. To determine the post-UV viability in some time-course experiments, irradiated and unirradiated cells were incubated for an additional 5, 7, or 10 days.

Post-x-ray survival experiments were performed as described previously [26] except that stock cultures were diluted with fresh medium to give a cell concentration of approximately 3×10^5/ml.

Survival Parameters and Statistical Analysis

The postirradiation viability ratio of the lymphoblastoid lines was calculated by dividing the concentration of viable cells in an irradiated culture on the third postirradiation day by the concentration of viable

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Abbreviations:

CS: Cockayne syndrome

D_0: dose reducing survival from any point on the exponential portion of the survival curve to 37% of that point

XP: xeroderma pigmentosum

TABLE I. *Clinical and laboratory characterization of lymphoblastoid line donors*

Cell donor[a]	Designation: Cell line: Lymphoblastoid	Designation: Cell line: Fibroblast	Diagnosis	Age	Sex	Complementation group: CS	Complementation group: XP	Acute sun sensitivity	Comment	Reference
CS2BE	GM 1712	GM 1098	CS	21	M	B		+	Typical CS	8,9,17
CS3BE	GM 1857	GM 1856	CS	13	M	A		+	Typical CS	8,9,17
CS1FABE	RB 5325	RB 5324	CS	5	M			?[b]	Typical CS	18[c]
Atypical CS	GM 2964	GM 2965	CS	25	F	A		+	Atypical CS	10,19
CSHM1BE	GM 2474		CS het[d]	29	M				Clinically normal father of CS1BE	
CSHM1FABE	RB 5323	RB 5322	CS het	30	M				Clinically normal father of CS1FABE	
XP-CS-1 (XP11BE) (CS4BE)	GM 2252		XP-CS	31	F	C	B	+	Affected with both XP and typical CS	12,17,20
XP-CS-HF-1	GM 1855	GM 1854	XP-CS het	64	F				Clinically normal mother of XP-CS-1	
XP-CS-2 (XP-SC-8)	GM 3249	GM 3248	XP-CS	5	M		H	+	Affected with both XP and typical CS	21,22
XP12BE	GM 2250		XP	10	F		A	+		12,20,23
XPHF12BE	GM 5511	GM 5510	XP het	44	F				Clinically normal mother of XP12BE	
XPHM12BE	GM 5569	GM 5568	XP het	47	M				Clinically normal father of XP12BE	
XP20S	GM 2345	GM 4419	XP	8	F		A	+		24
XP3BE	GM 2248	GM 0030	XP	25	M		C	+		12,20,23
XP9BE	GM 2498	GM 0676	XP	16	M		C			12,20
XP17BE	GM 2253		XP	14	M		D	+		11

[a] The designation of CS2BE signifies the second CS patient who was studied clinically at, or whose cell line was studied at, the NIH, Bethesda, Maryland. BE, Bethesda, Maryland; FA, Fargo, North Dakota; OS, Osaka, Japan. Heterozygotes are indicated by the letter H, with male and female being designated by M and F, respectively. Alternative, previously published designations are shown in parentheses.

[b] No reliable history concerning the presence or absence of acute sun sensitivity could be obtained (personal communication, R. A. Brumback).

[c] The patient whose autopsy is described in this reference is the sister of patient CS1FABE.

[d] het = heterozygote.

TABLE II. *Clinical features of two typical CS patients and of the atypical CS patient*

	Typical CS patients[a]: CS2BE	Typical CS patients[a]: CS3BE	Atypical CS patient[b]
Age[c] (sex)	21 (M)	12 (M)	25 (F)
Age (yr) of clinical onset	1	1	5
Cachectic dwarfism	Severe	Severe	Mild
Height (cm)	84	105	145
Weight (kg)	7.3	14.4	32
Acute sun sensitivity	+	+	+
Retinal pigmentation	+	+	–
Optic atrophy	+	+	–
Sensorineural deafness	Severe	Severe	Mild
Mental status	At 3 yr 9 mo[d]: Binet IQ 66 (2 yr 5 mo)[e]; at 4 yr 10 mo: Binet IQ 62 (3 yr); at 21 yr: IQ untestable	At 5 yr 5 mo: Binet IQ 52 (3 yr 1 mo); at 12 yr 8 mo: Slosson IQ 31 (4 yr 1 mo)	Graduated from high school and attended junior college; IQ was 78 when tested in high school[f]
Normal pressure hydropcephalus	+	+	Late onset
Choreoathetosis	+	+	–
Ataxia	+	+	–
Gait disturbance	+	+	Minimal
Hyperreflexia and clonus	+	+	–
Incontinence (urinary and fecal)	+	+	–
Sexual development	Infantile	Infantile	Successful pregnancy

[a] Data from Brumback et al [17]; + = present.

[b] Data from Kennedy et al [19]; + = present; – = absent.

[c] Age at last clinical observation and/or age of skin biopsy and venipuncture (for establishing cell lines).

[d] Age at IQ testing.

[e] Mental age.

[f] The IQ test administered is not known.

cells in an unirradiated culture of the same line on the same day [16]. At least 4 replicate experiments were performed on each line.

For analysis of the dose-response curves, straight lines were fit by the method of least squares through the 4, 6, and 10 J/m^2 doses for the normal lines, through the 2 J/m^2 and all higher doses for the CS lines, and through the 1 J/m^2 and all higher doses for the XP and XP-CS lines. The D_0 value is the negative inverse of the slope of this straight line and corresponds to the dose of UV radiation which reduces survival from any point on the straight line to 37% of that point. The extrapolation number is the value on the Y axis at which the extrapolation of

the straight line portion of a survival curve intercepts the Y axis.

There was no correlation between the postirradiation viability ratio and either the donor age or the growth rate of unirradiated lines. The statistical analyses were performed using analysis of variance methods [27], and 2-sided p values are reported.

RESULTS

The survival of the lymphoblastoid lines after irradiation with 6 J/m^2 of UV radiation is graphed in Fig 1. The mean post-UV viability ratios of the 4 CS, the 5 XP, and the 2 XP-CS lines were each significantly less ($p < 10^{-3}$) than that of the normal controls (Fig 1). The 2 XP-CS lines had a mean post-UV viability ratio which was significantly less than that of the 4 CS lines ($p = 0.012$). The differences in post-UV viability among the 4 CS lines, including the line from the atypical patient, were not significant. The XP group C line GM 2498 (○) from patient XP9BE had a significantly higher post-UV viability ratio than each of the other XP lines ($p < 0.01$). The XP-CS-1 line GM 2252 (◒) was more sensitive to UV radiation than the XP-CS-2 line GM 3249 (◓) ($p = 0.01$). The CS, XP-CS, and XP lines were not hypersensitive to x-rays. The post-UV viability of the heterozygote lines (2 CS, 1 XP-CS, 2 XP) was within the normal range (Fig 1).

Fig 2 and Table III show the results of UV dose-response experiments. The 3 normal control lines had the highest survival at all doses tested (Fig 2). Each of their curves has a positive shoulder, i.e., an initial portion which extends to the 4 J/m^2 dose and which has little downward slope. The mean D_0 value for the normal lines was 7.5 (Table III). There were no significant differences among the D_0 or extrapolation values of the normal lines.

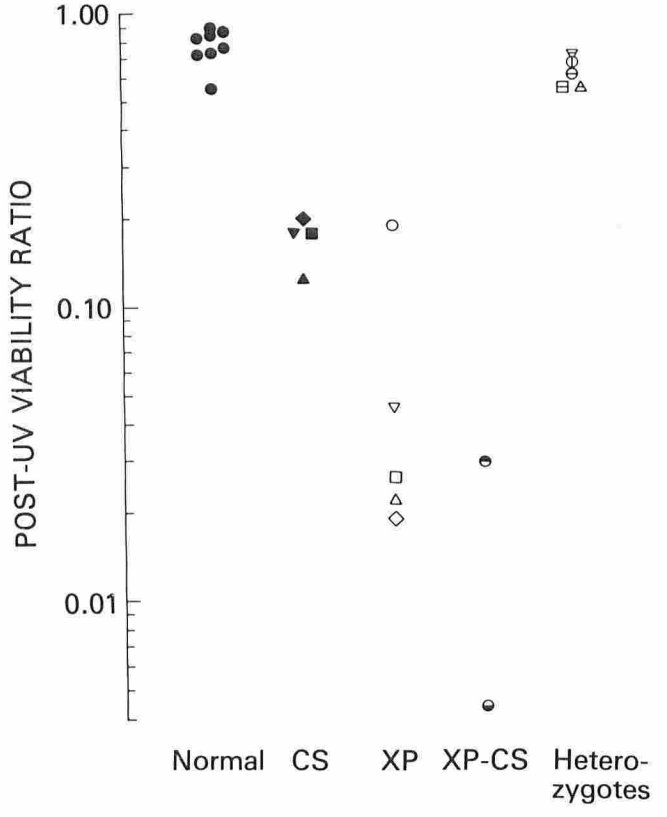

FIG 1. Survival of lymphoblastoid lines on the third day after exposure to 254-nm UV radiation (6 J/m^2). Each symbol represents the mean post-UV viability ratio of the replicate experiments performed on a cell line. Normal control lines, ●. CS: GM 1857, ◆; GM 1712, ▼; RB 5325, ■; GM 2964, ▲. XP: GM 2498, ○; GM 2250, ▽; GM 2253, □; GM 2345, △; GM 2248, ◇. XP-CS: GM 3249, ◓; GM 2252, ◒. Heterozygotes: RB 5323, ▽; GM 2474, △; GM 5569, ⊕; GM 5511, ⊖; GM 1855, ⊟.

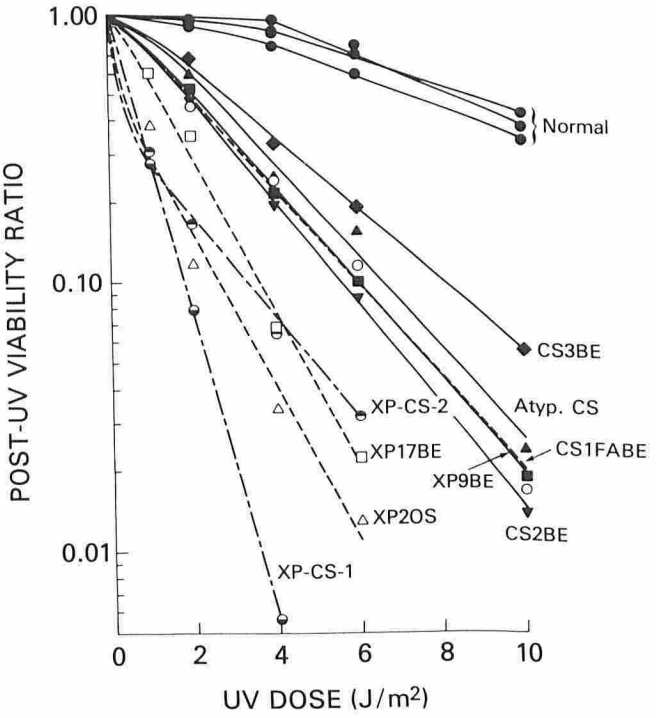

FIG 2. Dose-response curves of the post-UV survival of lymphoblastoid lines on the third day after irradiation with 254-nm UV radiation. Normal lines: GM 333, GM 536, GM 621. Symbols as in legend of Fig 1.

The dose-response curves for the 4 CS, 3 XP, and 2 XP-CS lines lacked the positive shoulder of the normal control lines and were below the normal curves at all doses tested. The 4 CS curves were grouped together near the curve for XP group C line GM 2498 from patient XP9BE. The mean D_0 value of 2.6 for the 4 CS lines (Table III) was significantly less than that of the normal lines ($p < 10^{-4}$). The D_0 value of 2.3 for GM 1712 (CS2BE) was less than the value of 3.3 for GM 1857 (CS3BE) ($p = 0.06$). A similar difference in relative survival was obtained after UV irradiation of the fibroblast lines from these 2 CS patients [8]. There were no significant differences among the extrapolation numbers of the 4 CS lines. Their mean extrapolation number of 1.2 was significantly less than that of the normal lines ($p = 0.008$). The dose-response curve of the atypical CS patient GM 2964 was between that of GM 1712 (CS2BE) and GM 1857 (CS3BE). The D_0 and extrapolation number for GM 2964 were not significantly different from the corresponding values for the other CS patients.

Dose-response curves were obtained for 3 of the XP lines. The group C line GM 2498 (from patient XP9BE) had a D_0 value of 2.5 (Table III) which was significantly higher than that of the other 2 XP lines ($p < 0.018$). The D_0 value of 1.6 for the XP group A line GM 2345 from patient XP20S was not significantly different from that of 1.5 for the group D line GM 2253 from patient XP17BE ($p > 0.50$). However, the dose-response curve for GM 2345 differed from that of GM 2253 in that it comprised 2 components: the first component is very steep and extends to the 1 J/m^2 dose; the second component, which is less steep, is exponential and extends from 2 J/m^2 through 6 J/m^2. The steep initial component of such a 2-component survival curve has been described as a "negative shoulder" [11], and the second component is characterized not only by its D_0 value but also by its extrapolation number of 0.5 which is significantly less than 1.0 ($p = 0.019$).

The curve for line GM 3249 from patient XP-CS-2 is also a 2-component curve, and its extrapolation number of 0.4 is significantly less than 1.0 ($p = 0.005$). The dose-response curve for line GM 2252 from patient XP-CS-1 had a D_0 value of 0.8

TABLE III. *Post-UV survival parameters of lymphoblastoid lines in dose-response experiments*

Lines	D_0[a]	Extrapolation number[b]
Normals		
GM 558	8.2	1.4
GM 333	7.2	1.5
GM 621	7.1	1.4
	7.5	1.5
	(± 0.4)	(± 0.03)
CS		
GM 1857	3.3	1.3
GM 2964	2.6	1.1
RB 5325	2.4	1.2
GM 1712	2.3	1.2
	2.6	1.2
	(± 0.2)	(± 0.04)
	$p < 10^{-4}$	$p = 0.008$
XP-CS		
GM 3249	2.4	0.4
GM 2252	0.8	0.9
	1.6	0.6
	(± 0.8)	(± 0.3)
	$p = 0.004$	$p = 0.026$
XP		
GM 2498	2.5	1.1
GM 2253	1.5	1.2
GM 2345	1.6	0.5
	1.9	0.9
	(± 0.3)	(± 0.2)
	$p = 0.0003$	$p = 0.087$

[a] The D_0 is the dose reducing survival from any point on the exponential portion of the survival curve to 37% of that point. Figures in parentheses represent SEM; p value for comparison with normal.

[b] The extrapolation number is the value of the Y axis at which the extension of the exponential portion of the survival curve intersects the Y axis. Figures in parentheses represent SEM; p value for comparison with normal.

which was significantly lower than that of any other line ($p < 0.05$). The mean D_0 value of 1.6 for these 2 XP-CS lines was significantly less than that of the 3 normal lines ($p = 0.004$). The D_0 for GM 3249 was in the range of the D_0 values of the CS lines; however, the D_0 for GM 2252 was significantly lower than the D_0 value of the 4 CS lines ($p = 0.001$). The mean extrapolation number of 0.6 for the 2 XP-CS lines was significantly less than that of the 3 normal lines ($p = 0.026$) and that of the 4 CS lines ($p = 0.05$).

Additional experiments were conducted with the atypical CS patient line GM 2964 and with the lines from 2 of the typical CS patients (GM 1857 and GM 1712). After these lines were irradiated with 10 J/m^2, there were no viable GM 1712 cells by the tenth postirradiation day, at which time all the other lines had surviving cells which were proliferating. When lines GM 1857 and GM 2964 were irradiated with 12 J/m^2, only the GM 1857 line had viable cells left by the tenth postirradiation day. Thus, these additional studies confirmed that the line from the atypical CS patient had a reactivity to UV radiation between that of the 2 typical CS patients.

DISCUSSION

CS is an autosomal recessive disease characterized by cachectic dwarfism, skeletal abnormalities, sexual infantilism, neurologic abnormalities, and acute sun sensitivity [1–6]. While there can be great differences in the occurrence of these clinical features among CS patients (see, for example, Table II comparing the atypical CS patient with the typical CS patients), no patients identified as having typical CS are known not to have had acute sun sensitivity. In contrast, many XP patients have never had acute sun sensitivity [12], and their cultured cells are less sensitive to the lethal effects of UV radiation than are cells from XP patients with acute sun sensitivity (Figs 1, 2) [11]. Since the degree of hypersensitivity of cultured cells from CS patients with acute sun sensitivity is similar to that of patient XP9BE (Figs 1, 2) who had no acute sun sensitivity (Table I), the hypersensitivity to UV radiation of CS cells in vitro and in vivo is likely to be caused by a different type of DNA repair defect than that of XP patients. As described below, important differences have been found between the CS and XP DNA repair defects.

There are several other clinical differences between CS and XP. CS patients, with the exception of those with both XP and CS, do not develop chronic actinic skin damage such as excessive freckles or sunlight-induced skin cancers. The extreme cachectic dwarfism of CS is not seen in XP patients, and XP patients lack the skeletal abnormalities seen in CS. The neurologic abnormalities of CS are principally due to demyelination, while those of XP are due to a primary neuronal degeneration [12]. Thus, the clinical manifestations of CS differ in most important respects from the clinical manifestations of XP. Cultured CS cells, like XP cells, are (1) hypersensitive to the lethal effects of UV radiation [6–9,28] and UV-mimetic chemicals [6,9,28], (2) abnormally sensitive to the UV radiation-induced inhibition of DNA and RNA synthesis [29], and (3) abnormal in the host-cell reactivation of UV-irradiated viruses [30–32]. However, in contrast to cultured XP cells, CS cells have normal rates of postreplication repair [9,10] and UV-induced unscheduled DNA synthesis [6–9]. Like XP cells, CS cells have a normal sensitivity to ionizing radiation, indicating that the hypersensitivity of CS lymphoblastoid lines to UV radiation is not a general response to all types of DNA-damaging agents.

In our study of the post-UV survival of 9 CS fibroblast lines [8], we observed the following features of the CS sensitivity to UV radiation: (1) each CS fibroblast line had significantly lower post-UV colony-forming ability than each normal line; (2) while the post-UV colony-forming ability of the least sensitive CS fibroblast line differed significantly from that of the most sensitive line, the differences in post-UV colony-forming ability among the CS fibroblast lines were less than those between XP fibroblast lines [11]; and (3) the hypersensitivity of CS fibroblast lines to UV radiation was not as great as that of the most sensitive XP lines [11]. We have now demonstrated similar features with CS lymphoblastoid lines: (1) each CS lymphoblastoid line was significantly more sensitive to UV radiation than each normal line; (2) while there can be significant differences in post-UV viability among the CS lymphoblastoid lines, these differences were less than those among XP lymphoblastoid lines [16]; furthermore, the CS patient (CS2BE) whose fibroblast line was significantly more sensitive than the fibroblast line from patient CS3BE [8] had a lymphoblastoid line that was more sensitive than the lymphoblastoid line from patient CS3BE (Fig 2); (3) the hypersensitivity of CS lymphoblastoid lines to UV radiation was not as great as that of the most sensitive XP lymphoblastoid lines (Fig 2). Thus, our study of CS lymphoblastoid lines reveals them to manifest the same qualitative and quantitative features of post-UV survival as CS fibroblast lines.

Our results show that the 1 XP-CS, the 2 CS, and the 2 XP obligate heterozygote lines were not hypersensitive to UV radiation. Therefore, the lymphoblastoid-line trypan-blue-exclusion assay cannot be used to identify such heterozygotes. Regarding such heterozygote detection, post-UV colony-forming ability studies with CS fibroblast lines have yielded conflicting results. Marshall et al [33] found no hypersensitivity in 2 CS heterozygote lines, while Wade and Chu [9] found a slight hypersensitivity in 4 heterozygote lines; however, in the latter study, only 2 normal lines were used. Since it is known that there can be significant differences in post-UV colony-forming ability among normal fibroblast lines [11,34], the claim by Wade and Chu [9] that CS heterozygote fibroblast lines are hypersensitive to UV radiation should be viewed with caution

until confirmed in a study using a larger number of normal lines.

In 1980, Kennedy et al [19] reported a patient with an atypical clinical picture of CS. While this patient, whose lymphoblastoid line is designated GM 2964, had acute sun sensitivity, she had only mild manifestations of CS (Table II). She graduated from high school, attended junior college, and had a successful pregnancy. Complementation studies [35] using fibroblasts from this atypical CS patient have shown her to be in CS complementation group A which also includes patient CS3BE; fusing her fibroblasts with those of CS3BE did not restore to normal the post-UV inhibition of RNA synthesis in the fused cells. Since this atypical patient's lymphoblastoid line GM 2964 is as sensitive to UV radiation as the lines from the typical CS patients (Figs 1, 2), we conclude that, with the exception of acute sun sensitivity, the severity and age of onset of the clinical manifestations we have evaluated in CS did not correlate with the degree of hypersensitivity of the patient's cultured cells. It should be noted, however, that the CS hypersensitivity to the UV type of DNA damaging agent may still be the etiology, directly or indirectly, of all the clinical manifestations of CS. The hypersensitivity to UV radiation of CS cells appears to be the result of a faulty DNA repair mechanism, for CS cells are unable to repair normally UV-irradiated viruses [30–32]. In order for defects in DNA repair to be clinically apparent, the DNA must be damaged. In the skin of CS and XP patients, this damage is caused by the UV radiation in sunlight. In the nervous system of XP patients and, presumably, also in the other non-sun-exposed affected tissues of CS patients, the DNA damage could be caused by endogenous metabolites and by spontaneous hydrolytic reactions (such as those described by Lindahl [36]). If the amount of damage varied among CS patients, different degrees of clinical manifestations would result even in the presence of the same quantitative defects in DNA repair.

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